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EDITORIAL

Let PEEP do the talking?

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Non-invasive ventilation (NIV) has an established role in various causes of acute, acute-on-chronic, and chronic ventilatory failure; however, its use in acute hypoxemic respiratory failure (AHRF) remains contentious. In part this reflects risks associated with failure of NIV, and delayed intubation, which are associated with increased mortality. Although these risks are particularly seen in patients with the acute respiratory distress syndrome (ARDS) [1, 2], NIV is both commonly used in patients with ARDS [3] and recognized in the Berlin criteria [4]. Of concern, the evidence supporting NIV use in patients with ARDS is based on relatively small samples [5].

Potential advantages of NIV in the management of patients with AHRF (Fig. 1) are mainly related to the avoidance of complications, including sedation, muscle paralysis, and ventilator-associated complications associated with endotracheal intubation and invasive mechanical ventilation.

Disadvantages of NIV stem from interface limitations (mask or helmet) and the lack of an artificial airway. Gas leaks at higher airway pressures combined with intolerance of the interface if too firmly applied mitigate against higher pressure application particularly when a mask is used. An artificial airway allows use of sedatives and paralyzing agents to help control ventilation, reduce asynchrony and respiratory drive, and improve patient comfort.

Patient self-inflicted lung injury (P-SILI) refers to effort-dependent lung injury resulting from high inspiratory drive, large tidal volumes, and transpulmonary pressures' swings [6]. Additionally, injury is exacerbated by regional pleural changes which can cause pendelluft where gas moves from nondependent (more recruited) lung to dependent (less recruited) lung [7]. Consequently, patients with AHRF breathing spontaneously are at-risk of P-SILI if their inspiratory effort remains excessive.

Both inspiratory and expiratory settings during NIV appear to influence the likelihood of P-SILI. In patients with AHRF NIV reduces drive and inspiratory effort but may simultaneously increase tidal volume [8]. Tonelli and coworkers [9] reported an inverse relationship between lung volume and inspiratory effort in patients with AHRF, and that an early reduction in inspiratory effort during NIV was associated with avoidance of intubation, consistent with less P-SILI. It is likely that recruitment and an increase in lung volume with NIV, associated with adequate positive end expiratory pressure (PEEP), reduced effort and subsequently P-SILI.

In a recent issue of the journal, Duan and coworkers [10] have addressed one aspect of this conundrum in a prospective, multicenter randomized trial ($n=380$) comparing lower PEEP (median 5 cmH2O) with higher PEEP (median 10 cmH2O) in patients with AHRF. Non-invasive ventilation failure (intubation, death, or withdrawal/refusal of NIV) occurred more commonly in the lower PEEP group (43% vs 32%), driven by patients with more severe AHRF. Patients with a PaO2/FiO2 ratio lower than 150 benefitted from higher PEEP. Within 72 h, the low PEEP group exhibited a lower PaO2/FiO2 (mean difference −31 mmHg, 95%CI: − 38 to − 24, $p<0.01$) and a reduced PaO2/FiO2 increment ($p=0.03$ for time*group interaction) consistent with the notion that higher PEEP reduced P-SILI.

Given the paucity of trial data comparing prescription of NIV in AHRF, this is potentially an important contribution; however, there was insufficient statistical power, and the manuscript does not specify whether other forms of respiratory support, such as high-flow nasal oxygen (HFNO), were used between NIV sessions. Applying

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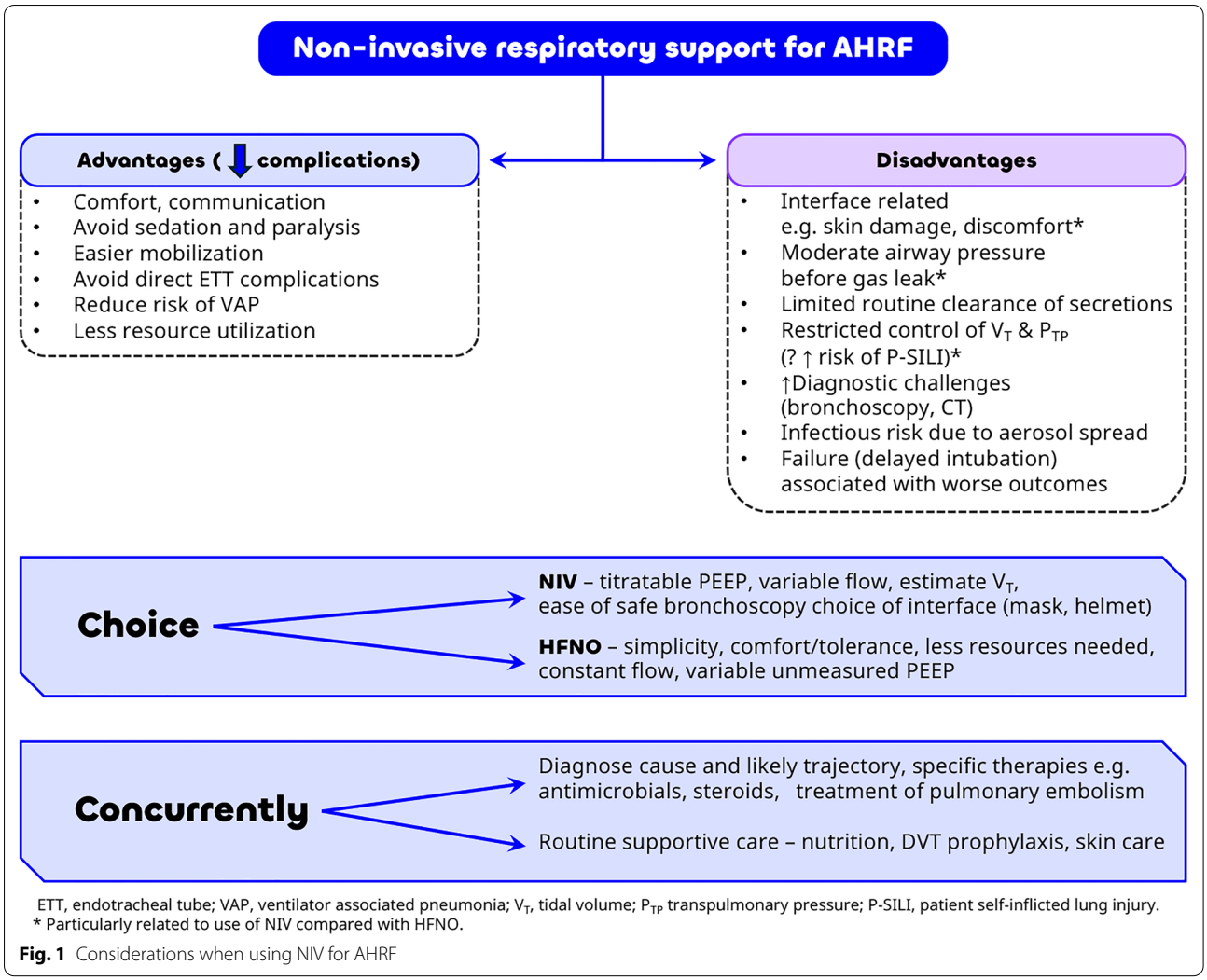
Non-invasive respiratory support for AHRF
Advantages (↓ complications)
Comfort, communication
Avoid sedation and paralysis
Easier mobilization
Avoid direct ETT complications
Reduce risk of VAP
Less resource utilization
Disadvantages
Interface related e.g. skin damage, discomfort*
Moderate airway pressure before gas leak*
Limited routine clearance of secretions
Restricted control of V_T & P_{TP} (? ↑ risk of P-SILI)*
↑Diagnostic challenges (bronchoscopy, CT)
Infectious risk due to aerosol spread
Failure (delayed intubation) associated with worse outcomes
Choice
NIV – titratable PEEP, variable flow, estimate V_T, ease of safe bronchoscopy choice of interface (mask, helmet)
HFNO – simplicity, comfort/tolerance, less resources needed, constant flow, variable unmeasured PEEP
Concurrently
Diagnose cause and likely trajectory, specific therapies e.g. antimicrobials, steroids, treatment of pulmonary embolism
Routine supportive care – nutrition, DVT prophylaxis, skin care
ETT, endotracheal tube; VAP, ventilator associated pneumonia; V_T, tidal volume; P_{TP} transpulmonary pressure; P-SILI, patient self-inflicted lung injury.
* Particularly related to use of NIV compared with HFNO.

Fig. 1 Considerations when using NIV for AHRF

higher PEEP using a face mask interface increases the likelihood of leakage due to an inadequate seal, often constrained by patient comfort. In this context, the helmet interface could offer an attractive alternative [11].

In contrast to ventilatory failure where the primary purpose of inspiratory support is to augment tidal and minute ventilation, in AHRF, inspiratory support targets reduced work of breathing and discomfort [8, 12]. In the current study, the lower PEEP arm had a higher inspiratory pressure support administered (median 9–10 cmH_2O vs 6 cmH_2O) and a slightly higher tidal volume (mean difference 0.8 ml/kg predicted body weight). As the level of inspiratory support was titrated to maintain the respiratory rate less than 25 breaths/min, the greater inspiratory support administered, and higher tidal volume might be anticipated as lower PEEP likely led to less recruitment, lower lung volume, and increased respiratory drive [9]. While this difference in tidal stretch seems relatively small, the increased drive, effort, and regional pleural pressure changes in the lower PEEP group [7, 8, 13, 14] may have resulted in P-SILI.

Noninferiority of high-flow nasal oxygen (HFNO) for AHRF (intubation or death within 7 days) compared to NIV recently reported in the RENOVATE Randomized Clinical Trial [15] might seem inconsistent with these findings as PEEP generated by HFNO is usually less than 5 cmH_2O. In the RENOVATE study [15], the NIV arm received an intermediate level of PEEP (8 cmH2O) with a tidal volume target of 6–9 ml/kg ideal body weight [15], albeit the delivered tidal volume was not reported. In addition, most of the patients studied did not appear to have severe AHRF perhaps biasing this comparison toward the HFNO arm. The impact of P-SILI is likely to be greater in severe AHRF where appropriately delivered NIV, particularly PEEP, may reduce respiratory drive and effort. In mild-to-moderate AHRF, the impact on P-SILI of lower PEEP and lack of inspiratory support with HFNO is likely less

important, which combined with its high patient tolerance may provide similar benefit to NIV.

A consistent message is developing when NIV or HFNO is used to manage AHRF. In addition to astute clinical judgment, beware when oxygenation is poor (PaO2/FiO2 < 150), do not delay intubation if patients are not improving and consider appropriate prescription of both expiratory and inspiratory support levels when using NIV. Contrasting the outcomes from the Duan [10] and RENOVATE (15), studies suggest that we need more data and that clarity in study design will be essential.

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Declarations

Conflict of interest
The authors declare no competing financial or non-financial interests.

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